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Pharmaceutical Medicine:
A National Security Risk?

Millions of Americans, including servicemembers, rely on drugs to stay healthy, yet the United States imports over 80% of its active ingredients used in domestic pharmaceutical production from foreign nations – predominantly China.[1,2] In this paper, we discuss a proprietary solution offered by Bright Path Labs to help address this national security and public health risk.

Background

The U.S.-China Economic and Security Review Commission recently released a report highlighting the United States' growing reliance on Chinese-manufactured pharmaceuticals and China's role as a global "active pharmaceutical ingredient" (API) producer.[3] APIs are the raw chemical components of drugs that "furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease."[4] APIs are requisite to manufacture pharmaceutical products, including generic drugs and vaccinations. Despite the critical role of APIs in drug production an estimated 80 percent of APIs used in domestic pharmaceutical production originate in foreign nations - predominantly China.[2]

The Chinese government makes significant investments in its pharmaceuticals production and systematically undercuts market prices, forcing U.S., European, and Indian producers out of business.[5] As a result, China is now the world's leading producer of APIs and accounts for more than 20 percent of total global output.[6] More concerning, the U.S. relies on imports of general antibiotics from China - including penicillin, the most basic component of antibiotics.[7] Hundreds of drugs Americans rely on to treat high blood pressure or heart or kidney conditions use APIs from China.[8] Many Chinese-made APIs can be found in generic drugs, which account for 89 percent of U.S. prescriptions.[9] Furthermore, pharmaceuticals used by the Department of Defense to protect servicemembers from nuclear and biological threats are also sourced in China.[10]

One expert summarized these concerns before Congress last month, “Medicines can be used as a weapon of war against the United States. In the hands of an adversary, they can be weaponized. Supplies can be withheld. Medicines can be made with lethal contaminants or sold without any real medicine in them, rendering them ineffective. These products can be distributed to specific targets. Detection is time-consuming at best, and virtually impossible at worst. The thousands of men and women on U.S. aircraft carriers in the South China Sea are dependent on the adversary for many of their essential medicines. Combat readiness and force protection are at risk with the military vulnerable to disruptions in supply and contaminated and toxic medicines.”[11]

“An overreliance on Chinese API exports raises the possibility that China could terminate or raise the cost of prescription drugs for millions of Americans, including servicemembers, in the event of escalating geopolitical tensions. This national security threat cannot be overstated. Should China seek to weaponize pharmaceuticals, by restricting exports to the United States, incorporating lethal ingredients in final products, or any other means, our domestic pharmaceutical industry is not prepared to handle mass shortages for domestic or military uses. Any interruption in the delivery of APIs or medicine would impact military readiness.”[1] Retired Brigadier General John Adams told NBC News recently, "basically we've outsourced our entire industry to China. That is a strategic vulnerability."[12]

Supply chain vulnerabilities and quality issues can also result when drug manufacturing is reliant on numerous foreign countries. For example, when drug makers source ingredients from other countries, it is difficult for U.S. regulators to police drug quality.[13] In one FDA study, of the 163 drugs that went into shortage between 2013 and 2017, 62 percent occurred as a result of **manufacturing or product quality problems**.[14] In general, there is a concerning lack of information surrounding the United States' importation of APIs and critical drugs.[1]

Pharmaceutical Industry Challenges

The most common cited factors for the significant increase in offshoring of API production primarily have to do with the fact that traditional drug production processes require a large factory site, have environmental liabilities, and can utilize a low-cost labor force.[15] In fact, according to Dr. Janet Woodcock of the FDA, a U.S.-based company could never offset the labor and other cost advantages that China enjoys simply by achieving higher productivity when using traditional pharmaceutical manufacturing techniques.[16]

For background, pharmaceutical manufacturing techniques, in general, haven't changed in 50 years.[17] Currently, the vast majority of APIs/pharmaceuticals are produced using three-dimensional volume-based systems, such as continuous stirred-tank reactors. Although these systems have improved incrementally over the years, they remain inefficient and costly to employ as they continue to suffer in critical areas such as rate and uniformity of mixing and precision of temperature control. These factors can greatly affect production rate, yield, and quality. The general start/stop nature of batch processing increases time delays, costs, and the risk of contamination, human error and purity variability.[18]

Shortcomings of employing volume-based (batch) systems are particularly evident in commercial scale-up or when production problems occur. In terms of scale-up, mixing and heating characteristics change with reactor size in these systems. Consequently, the scaling-up of a reaction from pilot to commercial levels can be difficult and can require a complete redesign of a production process. In the most difficult circumstances, scale-ups can take years to complete, consuming considerable economic resources.

As for production problems, valuable raw materials needed for a reaction are added in batches in these systems. Therefore, if a reaction fails, all of the materials in the tank must be discarded and the entire process restarted from the beginning. The annual cost estimates of these and related manufacturing wastes are staggering at over $50 billion per year and is the primary reason this industry has the worst E-Factor ranking of any at 25x-100x, which is an important measure for environmental impact equal to ratio of total waste (kg) / product (kg).[19, 20]

Continuous Manufacturing – Current State

In contrast to batch processing, end-to-end continuous manufacturing sends raw materials through an uninterrupted process until the final product is completed. There is general agreement across the industry (including the FDA) that continuous pharmaceutical manufacturing could help address industry challenges and provide tremendous benefits, such as:[21]

- Reduced costs from smaller equipment/facility footprint and lower operating expenses
- A faster manufacturing method (FDA estimates that some drugs which normally take a month to produce using conventional batch processing, may only take one day to make using a continuous manufacturing setup)
- Expected to be safer compared to batch methods by employing more rigorous process monitoring, lower solvent usage, and less handing leading to reduced human errors

- Potential for increased domestic manufacturing, which includes supply chain and security benefits (because continuous processes do not depend on low-cost labor, but instead on advanced manufacturing technology)
- Ability to respond much more rapidly to drug shortages and related challenges
- Potential for a significant improvement in process quality and consistency due to the ability to maintain state of control, low residence times, and no intermediate hold steps
- Reduction of stockpiles for necessary medicines, which are discarded on expiration, as more and more pharmaceuticals could be produced on demand

Despite a long-time acknowledgement of the benefits of continuous manufacturing in the industry, adoption has been slow and fragmented. Currently, for example, there are only 6 drugs, all small-molecule pharmaceuticals, that incorporate continuous manufacturing, but only partially and using basic technologies.[21]

We believe there are two primary barriers that have slowed industry's adoption of continuous manufacturing. First, is the issue of sunk costs and entrenched operating models (think gas-powered vs. electric cars). According to Badman et al, the challenge arises for a specific pharmaceutical product in justifying the transition from a known and installed (possibly fully depreciated) base technology with established business and regulatory processes to a new paradigm…..and because of the significant investment needed, approval for a transition must be made at very senior levels in companies, including the Board. However, investing in innovative technologies like continuous manufacturing along with new facilities is not a priority in the current business and regulatory environment. As a result, as medicines move to a smaller volume paradigm, the business case for major investments is challenging.[21]

Second, is the issue of scalability. Existing continuous flow reactor technologies (e.g., micro-coil, spinning disk, etc.) are not designed to readily scale from benchtop chemistry to commercial scale production. In general, these solutions attempt to take bulk fluids and constrict them which improves mixing up to a point, but quickly reaches a limit in mass transfer and thus, scalability. This is supported by a recent 2018 industry survey across numerous pharmaceutical and contract manufacturing organizations, none of whom indicated they had developed integrated capabilities to scale from drug substance to drug product manufacturing.[22] The challenges associated with 'scalability' are likely another reason the industry has been slow to adopt and invest in this new technology.

Relatedly, FDA rules have historically been seen as another barrier to update or modify existing processes for manufacturing pharmaceuticals - without having to endure a lengthy and rigorous regulatory review process. Fortunately, by recognizing the need to aid the efforts of pharmaceutical manufacturers, the FDA has opened the door for new and innovative technologies to increase the quality and efficiency of producing drugs.[15] In 2014, for example, the FDA launched the Emerging Technology Program to encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing. To reduce barriers to entry for advanced manufacturing, the Emerging Technology Team (ETT) provides a gateway for the early (pre-submission) discussion of innovative technologies and approaches, even before a candidate drug is identified.[15]

BPL Solution

Bright Path Laboratories, Inc ("BPL") is in a unique position to help address these challenges. First, we are a newer company without the burden of older plants, property, equipment, and technology and thus not hindered with an out-of-date operating model. Second, scalability is not an issue for our patented spinning-tube-in-tube ("STT®") reactors, since the parameters that control the (chemical) reactions don't change as the size of the reactors are increased. As explained in more detail below, we believe these factors along with our Green Chemistry approach are important differentiators for BPL and position us to potentially help address the challenges discussed in this paper.

The heart of our approach is centered on our proprietary STT® technology that allows us to decrease the time and costs associated with conventional batch manufacturing processes by:

i) accelerating the rates of chemical reactions;
ii) avoiding inefficiencies resulting from uneven mixing, temperature gradients, scale-up constraints, and excessive waste;
iii) controlling the quality of chemical processes in real-time which, when a problem is detected, can be immediately corrected and thus, reduce waste
iv) reduced environmental and physical footprint

The STT® reactors are able to overcome the shortcomings of volume-based (batch) chemical production systems by employing a proprietary highly sheared, two-dimensional flowing film format. The higher mixing "shear" in the STT® system translates to a more precise temperature control imparted by the thinness of the film which increases production rates and yields. Acceleration in the rate of reaction of up to three orders of magnitude and increases in product yield of up to seven-fold, have been observed.

Since our beginning, Green Chemistry has been a hallmark of BPL's vision and approach to chemical reaction and API route design, another important differentiator for BPL. We have demonstrated we can control the sustainability of a chemical process by focusing on the early synthesis design. By proactively selecting the green reaction pathways, we are able to decrease the number of synthesis steps and chemical reagents needed, separations, protection group additions/removals, and purification stages. Also, by limiting solvent usage, or using more environmentally benign solvents, we are able to decrease or eliminate the need for extensive solvent removal steps, purification, and recycling, as well as the purchasing of the solvent. This not only leads to obvious advantages from a synthesis and process standpoint, but also brings significant cost and energy savings as well as worker safety and community benefits.

The premise of employing a Green Chemistry approach is to contribute to the development of sustainable manufacturing processes. For pharmaceuticals, this means simplifying the reaction strategy, minimizing resources, lowering capital equipment needs and energy consumption, decreasing process manufacturing time and improving human health and environmental impacts throughout the product's entire life cycle. We are proud of our leadership in this area and the academic and lab accomplishments we've achieved, which typically results in chemistries being produced with E-Factors in the range of 1-2x.

Opportunity

The pharmaceutical industry has a significant responsibility in helping to meet patients' medical needs. Access to quality medicine is essential for improved care, quality of life and national security. BPL's mission is to bring our disruptive manufacturing technology to the pharmaceutical industry where we can have a significant impact in providing high quality medicines to consumers that are available, affordable and secure (traceable). As an American owned and operated company, we are also well positioned to help reduce the above-mentioned national security, supply chain, and drug shortage risks that arise from today's substantial offshoring of API production. Please don't hesitate to reach out to us to learn more or to identify how we can collaborate to meet our shared goals.

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